## Remarks

Upon entry of the foregoing remarks, claims 88-90, 98, 105, 109, 11 6-1 19, 160, 163, 164 and 167 are pending in this application. Claims 99-1 04, 106-1 08, 11 0- 1 15, 127-1 30, 138-1 41, 149-1 52, 1 62, 166, 168, 170, 171, 173, 174, 176, 177, 179, 180, 182, 183 and 185-1 99 have been withdrawn from consideration as being directed to a non-elected invention. Claims 1-87, 91 -97, 120-1 26, 131 -1 37, 142-1 48, 153-1 59, 161, 165, 169, 172, 175, 178, 181 and 184 have been previously canceled without prejudice or disclaimer of the canceled subject matter. Applicant maintains the right to file one or more continuation or divisional applications on any canceled subject matter.

*The Claimed Invention*

The pending claims are drawn to a composition consisting of an antigen with 3-O-deacylated monophosphoryl lipid A or monophosphoryl lipid A in combination with granulocyte macrophage colony stimulating factor (GM-CSF), together with a diluent or carrier that can be used in the form of a stable oil-in water emulsion. This adjuvant-cytokine formulation is used to enhance the immune response in a vertebrate host to an antigen, wherein the antigen is derived from a pathogenic virus, particularly polypeptides, peptides or fragments derived from the human immunodeficiency virus (HIV).

Additionally, methods are claimed to elicit an immune response by administering said composition to a host wherein the immune response elicits cytotoxic T- lymphocytes (CTL).

The invention described herein discloses that the combination of an antigen, a selected cytokine, and an immunostimulating complex lipid adjuvant, MPL, increases the immune response specific for the antigen. The invention is exemplified in a model system using peptide antigens derived from HIV. The claimed antigen-cytokine-adjuvant combination induces high titers of antigen-specific and virus neutralizing antibody and also induces good cellular responses as determined through induction of CTL.

***Claim Rejections -35 USC §103(a)***

Claims 88-90 stand rejected under 35 USC §103(a) as allegedly being obvious over Ulrich et al. (Vaccine Design. Plenum Press, New York, N.Y., pg. 495-523, hereafter "Ulrich") and Disis et al. (Blood, 1996; Vol.88, No.1:202-210,hereafter "Disis"). The Examiner contends that Ulrich taught that the immunostimulant MPL delivered in aqueous admixtures, in oil and water emulsions, or in liposomal vehicles, has adjuvant activity. The Examiner also asserts that Disis taught that GM-CSF is an effective adjuvant. It is the Examiner's opinion that both Ulrich and Disis teach adjuvant compositions that would allegedly be prima facie obvious to combine to yield Applicant's claimed invention.

Claims 88, 98 and 116-119 stand rejected under 35 USC §103(a) as allegedly being obvious over Ulrich and Disis as applied to claim 88, in view of Bartlett et al. (hereafter "Bartlett). Bartlett is cited for teaching the same amino acid sequence as SEQ ID NO:2 of the present invention to elicit an HIV-antigen specific response. The Examiner contends that it would have been prima facie obvious for one skilled in the art at the time the invention was made to combine the adjuvant composition of Ulrich and Disis with the HIV antigen of Bartlett.

Claims 88, 98, 105, 109, 116, 160, 163-164 and 167 stand rejected under 35 USC §103(a) as allegedly being obvious over Ulrich and Disis in view of Bartlett, as applied to claims 88, 98 and 116. The Examiner asserts the opinion that in addition to the previous rejections regarding Applicant's claimed composition that the administration of the antigen in Bartlett would necessarily induce a CTL response in the subject because the antigen of Bartlett contains CTL specific epitopes and would necessarily induce a CTL response. Applicant respectfully disagrees and traverses these rejections.

In the office action dated March 19, 2008, the Examiner stated that Applicant's arguments were not commensurate in scope with the Examiner's rejection of Claims 88-90 based on the fact that the claimed invention is directed at a composition consisting of an antigen, an adjuvant and a cytokine, not a method of enhancing the immune response induced by MPL and an antigen with the addition of GM-CSF. Nowhere in the arguments of the rejection of Claims 88-90 did Applicant refer to a method of enhancing the immune response. Applicant argued against the Examiner's insistence on equating

an adjuvant and a cytokine as art- recognized equivalents, which will be fully addressed below. Applicant argued that a cytokine and an adjuvant are functionally different, therefore they could not be art recognized equivalents. Applicant did not argue the method of eliciting an immune response. Applicant continues to strongly disagree with the Examiner's contention and maintains that a cytokine and an adjuvant are not equivalents and all arguments are, in fact, commensurate in scope with the Examiner's rejection.

A key aspect of all three sets of rejections listed above is the Examiner's continued assertion that MPL and GM-CSF are "art-recognized" equivalents, as stated above. The Examiner contends that because MPL and GM-CSF are both allegedly "adjuvants", it would have been obvious to one of ordinary skill in the art to combine them into one composition to enhance the immune response against an antigen of interest. Applicant respectfully disagrees and traverses these rejections.

Ulrich discloses that the immunostimulant complex lipid MPL delivered in aqueous admixtures, in oil-in-water emulsions, or in liposomal vehicles, has adjuvant activity. Nowhere in this reference do the authors teach or suggest the combination of antigen and MPL and a cytokine, specifically GM-CSF. Disis discloses GM-CSF to be an effective immunomodulator, but without any teaching or suggestion to combine GM-CSF with any other adjuvant or cytokine.

The Applicant submits that there is nothing in Ulrich or Disis that would prompt the skilled artisan to combine an antigen with the claimed adjuvant combination of MPL and a cytokine, specifically GM-CSF. The Examiner does not point to specific information in Disis that suggests its combination with Ulrich to yield the claimed invention. Instead, the Examiner has cited a passing reference to the combination of MPL and TDM on page 510 of Ulrich. Applicant would like to point out that the claimed invention of the present application is directed to the combination of an adjuvant and a cytokine. TDM is not a cytokine. TDM is a general activator that causes a severe reaction in subjects upon administration. TDM is vastly different than a cytokine and should not be equated as such. There is no teaching or suggestion in Ulrich to combine MPL with a cytokine or lymphokine, and more specifically GM-CSF. GM-CSF activates the immune system in a very specific manner using pathways within the immune system vastly different that the general inflammatory response generated by TDM. Besides, as

stated below, there is no way of predicting a synergistic reaction between MPL and GM-CSF merely by reading that combining MPL and TDM enhance an immune response.

The Applicant maintains that the Examiner merely notes how the two references **can** be combined to read on the claimed invention without any explanation as to **why** the skilled artisan would be motivated to combine them. This reference-by reference, limitation-by-limitation analysis wholly fails to demonstrate how the cited references teach or suggest the combination claimed in the present invention. As stated in *Bausch & Lomb v. Barnes-Hind/Hydrocurve, Inc., 230* USPQ 416, 419 (Fed. Cir. 1986), "It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art."

The individual references cited by the Examiner establish the individual properties of the individual elements without any teaching or suggestion to combine these elements. There is nothing in the cited references to suggest to the skilled artisan - not to the Examiner having Applicant's specification in hand with legally impermissible hindsight - that the adjuvant combination of MPL plus GM-CSF would have been obvious at the time the claimed invention was made.

In lieu of an explanation as to why one of skill in the art would be motivated to combine the references, the Examiner instead continues to cite *In re Kerkhoven* and MPEP §2144.06 in support of this rejection. *In re Kerkhoven,* and the related section of the MPEP, stand for the proposition that it is prima facie obvious to combine two compositions, each of which are taught by the prior art, to form a third composition which is useful for the same purpose. MPEP §2144.06, "Art Recognized Equivalents for the Same Purpose: Combining Equivalent Known for the Same Purpose.", *In re Kerkhoven* presented a case where the claims were related to a process of preparing a "new" spray-dried detergent by mixing two conventional spray-dried detergents together. The new combination was held as being prima facie obvious based on two equivalent compositions being added together to form a third composition useful for the same purpose. In relying on *In re Kerkhoven*, the Examiner continues to conclude that the Applicant's invention is the combination of two compositions that are art-recognized equivalents . Applicant strongly disagrees.

Applicant maintains that an adjuvant and a cytokine are not art-recognized equivalents. Adjuvants are defined as a group of diverse heterogeneous compounds used to evoke or increase an immune response to an antigen. Adjuvants belong to a class of compositions that would broadly be defined as "any molecule or substance that is able to favor or amplify a particular situation in the cascade of immunological events (Virgil EJC Schijn, "Immunological Concepts of Vaccine Adjuvant Activity", Current Opinion in Immunology 2000, 12: 456-463, (as provided in the supplemental Information Disclosure Statement that accompanies this response)). This cascade of immunological events, as stated, is individual for every adjuvant. Different sets of cytokines and lymphokines are activated upon exposure to an adjuvant. Different pathways and interactions of these pathways are therefore activated. Adjuvants are separated into different functional categories that are used to classify adjuvants with different activities. For example, some classes of adjuvants localize an antigen in the lymph node where there is a facilitation of antigen uptake and presentation by antigen presenting cells (APCs). Other adjuvants have a depot effect whereby there is a prolonged antigen presentation at the injection site. Yet other adjuvants, cause an increase in signaling of pathogen recognition receptors (PRR) on APCs, which then direct innate immune cells to respond to the antigen. These are only a few examples of the different categories of adjuvants, there are hundreds of individual adjuvants with different functions. Clearly, adjuvants are a very broad class of molecules whose function, mechanism and characteristics differ greatly.

Cytokines are molecules that have very specific functions (Chapter 12 "Cytokines" from Cellular and Molecular Immunology, 2nd edition; pages 240-241, (as provided in the supplemental Information Disclosure Statement that accompanies this response)). Cytokines are defined by their individual functions, which are broken down into categories, namely: 1) mediators of natural immunity; 2) regulators of lymphocyte activation; growth and differentiation; 3) regulators of immune mediated inflammation; and 4) stimulators of immature leukocyte growth and differentiation. GM-CSF was known to act on bone marrow progenitor cells already committed to develop into leukocytes discussed on page 259. *Id.*

Clearly, complex lipid adjuvants and cytokines are different classes of compositions and are not art-recognized equivalents. It is respectfully submitted that the

Examiner has continued to inappropriately equate the broad concepts of immune modulation and adjuvants to assert that all adjuvants and cytokines are art-recognized equivalents. Based on the fact that the Applicant's claimed invention is not the mixing of two equivalents, the Applicant respectfully submits that the Examiner's reliance on MPEP §2144.06 and *In re Kerkhoven* is therefore improper.

Applicant maintains that the Examiner has not presented a case as to the scientific evidence that the skilled artisan would use to combine the teachings of the references to yield the claimed invention, as stated in the current office action. Applicant continues to maintain, with supporting argument from the submitted Declaration of Michael Hagen, Ph.D, under 37 CFR §1.132 which accompanies this response, that the Examiner's rejection of Applicant's claimed invention based on Kerkhoven is improper.

As stated in paragraph 7 of the Declaration of Michael Hagen, Ph.D, under 37 CFR §1.132 which accompanies this response, one skilled in the field of Immunology would immediately recognize that a cytokine (GM-CSF) and a complex lipid (MPL) are not "art-recognized equivalents" compositions. Also, as stated in paragraph 7 of the Declaration of Michael Hagen, Ph.D, under 37 CFR §1.132, "Adjuvants and cytokines have inherently different mechanisms of action and, in my opinion, would not be considered as equivalents. An adjuvant works through the stimulation of a general immune response and can activate one or many different cytokines or chemokines during its course of action. Every cytokine or chemokine individually stimulates different pathways within the immune system. All of these pathways are different and every response by the immune system is different based on the adjuvant(s) used and the antigen administered with it. Cytokines, when administered to a subject, stimulate only one pathway. During the combination of an adjuvant and a cytokine, because of the different pathways involved, the immune response is unpredictable regardless of the individual mechanisms of action of the adjuvant and the cytokine. The other variable is the antigen itself. The administration of different antigens will yield a different immune response based on the individual properties of that particular antigen. The immune response generated from the combination of an antigen and an adjuvant and/or a cytokine is, again, unpredictable. There is no way in advance of knowing what will work until the appropriate experiments are completed."

Additionally, Applicant maintains that the Examiner's continued assertion that a response of a combination of an adjuvant and a cytokine is predictable is invalid. The Examiner has continued to insist that it would be obvious to combine art elements to yield "predictable results". Applicant maintains that there is nothing predictable about the combination of Applicant's claimed invention.

Applicants have previously noted that Boon et al. (WO 98/57659, hereafter "Boon") states that GM-CSF added to a combination of MPL and QS21 was "unable to enhance the effect of the QS21/MPL adjuvant". Boon is concerned with identifying the cytokine that would best augment the already known adjuvant combination of MPL and the saponin QS-21. Boon teaches that GM-CSF does not enhance the effect of an adjuvant formulation that comprises MPL adjuvant. The skilled artisan upon reading Boon would have been compelled to avoid addition of GM-CSF with MPL.

The Examiner noted that the adjuvant formulation of Boon comprises more ingredients than those being claimed and rendered obvious by the cited art. The Examiner has also noted in the Office action dated March 19, 2008 on the bottom of page 12 that " the teaching of this reference has been noted, however any allegation of Boon et al. as a teaching away from the claimed invention is moot for the rejection is not made over Boon". Applicant maintains that the MPL, QS-21 and GM-CSF combination of Boon argues firmly against the Examiner's continued insistence that the combination of **any** adjuvants, cytokines or a mix of adjuvants, cytokines and peptides, as in the Applicant's invention, should therefore work in combination. The Examiner asserts that all of these compositions are equivalents and that any combination should work to enhance an immune response to an antigen. Applicant maintains that if, as the Examiner states, that all of these compositions are indeed equivalents and would be obvious to combine to form a third composition used for the same purpose, then Boon's addition of GM-CSF to a MPL/QS21 adjuvant combination should have enhanced the immune response. GM-CSF did not enhance the response. The Examiner has continued to underscore Applicant's argument that not all combinations of adjuvants will work in combination to enhance the immune response to an antigen.

As an additional argument, Applicant would like to further submit another reference that definitively shows that the notion that any adjuvant with any antigen with or without another immunomodulator will obviously produce an enhanced immune

response is invalid. Applicant submits Mishkin et al. US patent 6,488,936 (as provided in the supplemental Information Disclosure Statement that accompanies this response) to use as an example that every combination of adjuvant with antigen will not predictably work to enhance an immune response. Data shown in Mishkin et al. clearly shows examples of adjuvant combinations that **do not** enhance an immune response when combined. Applicant would like to draw the Examiner's attention to Table 1a "IL-12 Enhancement of the Plasma IgG Antibody Response to HSH-gD Immunization " which shows data relating to an experiment whereby glycoprotein D was administered with IL-12 at different concentrations on Day 28. Lower in the same column data shows glycoprotein D plus adjuvant administered with IL-12 at different concentrations. IgG titers were measured in all cases. The data clearly shows that at most the immune response against glycoprotein D was enhanced merely twofold with the combination of IL-12 with $AlPO_4$. This is an additive result, not a synergistic result. If the Examiner's arguments that any combination of adjuvant and cytokine would synergistically increase and immune response to an antigen, then the data in Mishkin et al. would have clearly demonstrated this.

In contrast, Applicant also wishes to point to the data in the present application. Applicant maintains that the unique combination of MPL and GMCSF along with the antigen denoted by SEQ ID.NO. 1 produces an enhanced effect on the immune response which is synergistic, not merely additive, as stated on page 20 of the present specification. For example, Applicant would like to point to the data exemplified on page 46 of the present specification. The table shows each of the endpoint titers of IgG at weeks 4, 6 and 8. For example at the week 4 endpoint titers, 5 μg of antigen alone was administered to mice, which yielded less than a 100 IgG titer. The results were the same when GM-CSF and MPL-SE were administered alone with the antigen. In contrast, when MPL-SE, GM-CSF and the antigen were administered together the resulting titer was measured at 14, 824, which is seventy-four times higher than any additive effect. The same results are seen at week 6 and week 8. In fact, this synergistic response can be seen throughout the present specification in the Examples section. If the Examiner was correct in the statement that all combinations of adjuvants would work to enhance an immune response, Applicant wishes to contrast the data presented in the present specification and compare this to the data in Table 1a of Exhibit A. The data clearly

disputes this statement that all cytokines, adjuvants and combinations thereof are predictable in their actions during combination.

Applicant also maintains that the Examiner has still failed to articulate why it would have been apparent to one skilled in the art to combine the elements recited in the pending claims. Most, if not all, inventions arise from a combination of old elements. *See In re Rouffet,* 149 F.3d 1350, 1357, 47 USPQ2d 1453,1457 (Fed. Cir. 1998). Thus, every element of a claimed invention may often be found in the prior art. *Id.* However, identification in the prior art of each individual part claimed is insufficient to defeat patentability of the whole claimed invention. *Id.* Rather, to establish obviousness based on a combination of elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant. *See In re Dance,* 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998); *In re Gordon,* 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984).

The motivation, suggestion or teaching may be found in explicit or implicit teachings within the references themselves, from the ordinary knowledge of those skilled in the art, or from the nature of the problem to be solved. *See WMS Gaming, Inc. v. International Game Tech.,* 51 USPQ2d 1385, 1397 (Fed. Cir. 1999). However, there still must be evidence that "a skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed." *In re Rouffet,* 47 USPQ2d at 1456; *see also In re Kotzab,* 55 USPQ2d 1313, 1317 (Fed. Cir. 2000) ("[a] rejection cannot be predicated on the mere identification ... of individual components of claimed limitations. Rather, particular findings must be made as to the reason the skilled artisan, *with no knowledge of the claimed invention,* would have selected these components for combination in the manner claimed.").

Additionally, MPEP 2143.01 IV clearly points out that "a statement that modification of the prior art to meet the claimed invention would have been 'well within the ordinary skill of the art at the time the claimed invention was made' because the references contained all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teaching of the reference.". *Ex parte Levengood*, 28 USPQ2d

1300 (Bd. Pat. App. & Inter. 1993) See also In *re Kotzab*, 217 F. 3d 1365, 1371, 55 USPQ2d 1313, 1318 (Fed. Cir. 2000).

Applicant maintains that there would have been no way to predict this clearly unexpected, synergistic effect. There could have been no reasonable expectation of success previous to actual experimentation. In MPEP §2141 "Examination Guidelines for Determining Obviousness Under 35 USC §103(a)", it states that the Supreme Court reaffirmed principles based on its precedent that "the combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results" *KSR International Corporation v. Teleflex In. (KSR), 550 U.S. __, 83 USPQ2d 1395 (2007).* Again, in MPEP §2143 "Examples of Basic Requirements of a Prima Facie Case of Obviousness" one of the "Exemplary Rationales" that may support a conclusion of obviousness includes combining prior art elements to yield predictable results. Again, Applicant wishes to respectfully maintain that in light of the arguments presented regarding Applicant's data, as well as the refuting Exhibit A showing lack of predictability of adjuvant and cytokine combinations and, particularly, to the Declaration under 37 CFR 1.132 that the rejection under 103(a) is improper and should be withdrawn.

Based on the foregoing, it is respectfully submitted that claims 88-90 are not obvious in view of the cited references and withdrawal of this rejection is requested.

As noted above, claims 88, 98 and 116-119 additionally stand rejected under 35 USC §103(a) as allegedly being obvious over Ulrich and Disis as applied to claim 88, in view of Bartlett. Bartlett is cited for teaching the same amino acid sequence as SEQ ID NO:2 of the present invention to elicit an HIV-antigen specific response. It is the Examiner's opinion that it would have been prima facie obvious for one skilled in the art at the time the invention was made to combine the adjuvant composition of Ulrich and Disis with the HIV antigen of Bartlett. The applicant respectfully disagrees and traverses the rejection.

The Examiner has further cited Bartlett to reject the claims that are limited to an HIV peptide. Applicant maintains that Bartlett merely evaluates the immunogenicity of polyvalent HIV envelope synthetic peptide immunogen in the presence of one adjuvant (incomplete Freund's adjuvant). The peptide taught in Bartlett, C4-V3, has the same amino acid sequence set forth in Applicant's SEQ ID NO:2. The combination of Ulrich

and Disis, as already stated, does not render the claimed invention obvious and adding Bartlett's observations on a particular peptide does not change this result. There is nothing in the cited reference to suggest to the skilled artisan that the adjuvant combination of MPL and GM-CSF would have been obvious alone with or without the addition the particular peptide taught in Bartlett. Applicant respectfully submits that the Examiner's rejection is invalid and should be withdrawn.

Based on the foregoing, it is respectfully submitted that claims 88, 98 and 116-119 are not obvious in view of the cited references and withdrawal of this rejection is requested.

As noted above claims 88, 98, 105, 109, 116, 160, 163-164 and 167 additionally stand rejected under 35 USC §103(a) as allegedly being obvious over Ulrich and Disis in view of Bartlett, as applied to claims 88, 98 and 116. It is the Examiner's opinion that, in addition to the previous rejections regarding Applicant's claimed composition, the administration of the antigen in Bartlett would necessarily induce a CTL response in the subject, because the antigen of Bartlett contains CTL specific epitopes and would necessarily induce a CTL response. Applicant respectfully disagrees and traverses the rejection.

As previously discussed, the combination of teachings from Ulrich and Disis in view of Bartlett does not render the claimed invention obvious. Since independent claim 88 is not rendered obvious by the combination of cited references, dependent claims 98, 105, 109, 1 16, 160, 163, 164 and 167 are likewise not obvious. Applicant respectfully submits that the Examiner's rejection is invalid and should be withdrawn.

Based on the foregoing, it is respectfully submitted that claims 88, 98, 105, 109, 116, 160, 163-164 and 167 are not obvious in view of the cited references and withdrawal of this rejection is requested.

In summary, the Examiner continues to improperly apply *In re Kerkhoven* and MPEP §2144.06 by taking the broad terms "adjuvant" and "cytokine" and concluding that these two different elements of Applicant's claimed invention are art-recognized equivalents when clearly they are not, as argued and supported by the submitted Declaration. According to MPEP §716.01 "Generally Applicable Criteria" regarding Declarations under 37 CFR § 1.132, the Examiner is under the obligation to fully

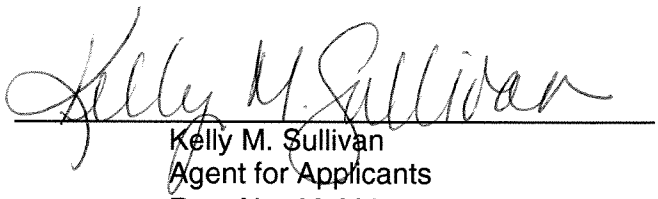
consider the Declaration submitted and sufficiently comment upon it's contents consistent with the guidelines provided under MPEP §1302.14.

Additionally, the Examiner has failed to establish a *prima facie* case of obviousness by failing to meet the standard of the KSR decision. The Examiner has failed to articulate why someone skilled in the art would have predicted the utility of the combination of elements in Applicant's claimed invention. In light of the arguments presented herein as well as the refuting references showing lack of predictability of adjuvant and cytokine combinations and, in particular, the Declaration under 37 CFR 1.132, Applicant respectfully maintains that the rejection under 103(a) is improper and should be withdrawn.

**Conclusion**

In conclusion, this reply is believed to be a full response to the outstanding Office Action. Should any issues remain outstanding or if there are any questions concerning this paper, or the application in general, the Examiner is invited to telephone the undersigned representative at the Examiner's earliest convenience.

Respectfully submitted,



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